	Type	L #	Hits	Search Text	DBs
1	BRS	L1	17	(red adj blood adj cell) same (nitric adj oxide$ or cysno)	USPAT
2	BRS	L2	7	nitrosohemoglobin	USPAT
3	BRS	L4	5	l3 and deoxygen$	USPAT
4	BRS	L5	1	l3 and deoxygen$ adj erythro$	USPAT
5	BRS	L6	0	6153186.pn/	USPAT
6	BRS	L8	0	l7 and deoxygenat$ adj eryth$	USPAT
7	BRS	L7	1	"6153186".pn.	USPAT
8	BRS	L3	7	nitrosohemoglobin or SNO adj hb	USPAT

	Time Stamp	Comments	Error Definition	Errors
1	2004/11/22 18:28			
2	2004/11/22 18:46			
3	2004/11/22 18:50			
4	2004/11/22 19:04			
5	2004/11/22 19:04			
6	2004/11/22 19:12			
7	2004/11/22 19:21			
8	2004/11/22 19:21			

	Type	Hits	Search Text
1	BRS	267	oxyhemoglobin same (NO or nitric adj oxide)
2	BRS	37	oxyhemoglobin same (nitric adj oxide)
3	BRS	7	nitrosohemo$
4	BRS	0	SNOHB same eryth$

	DBs	Time Stamp	Comments	Error Definition
1	USPAT	2004/11/22 12:22		
2	USPAT	2004/11/22 12:24		
3	USPAT	2004/11/22 13:37		
4	USPAT	2004/11/22 18:24		

	Errors	Ref #
1		S300
2		S301
3		S302
4		S303

```
=> s nitrosohemog?(P)(nitric oxide)
          0*  FILE ADISNEWS
          0*  FILE ANTE
          0*  FILE AQUALINE
          1   FILE BIOBUSINESS
          0*  FILE BIOCOMMERCE
          2*  FILE BIOENG
         58   FILE BIOSIS
          0*  FILE BIOTECHABS
          0*  FILE BIOTECHDS
         19*  FILE BIOTECHNO
          2   FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          3   FILE DDFU
          3   FILE DISSABS
  28 FILES SEARCHED...
          4   FILE DRUGU
         31   FILE EMBASE
         35*  FILE ESBIOBASE
          7*  FILE FEDRIP
          0*  FILE FOMAD
          0*  FILE FOREGE
          0*  FILE FROSTI
          0*  FILE FSTA
          6   FILE IFIPAT
  45 FILES SEARCHED...
          1   FILE JICST-EPLUS
          0*  FILE KOSMET
          0*  FILE MEDICONF
         33   FILE MEDLINE
          1*  FILE NTIS
          0*  FILE NUTRACEUT
          7*  FILE PASCAL
          0*  FILE PHARMAML
         95   FILE SCISEARCH
          8   FILE TOXCENTER
          9   FILE USPATFULL
  70 FILES SEARCHED...
          0*  FILE WATER
          2   FILE WPIDS
  74 FILES SEARCHED...
          2   FILE WPINDEX

  21 FILES HAVE ONE OR MORE ANSWERS,   75 FILES SEARCHED IN STNINDEX

L1   QUE NITROSOHEMOG?(P)(NITRIC OXIDE)
```

L3 ANSWER 1 OF 33 MEDLINE on STN
AN 2004499290 IN-PROCESS
DN PubMed ID: 15367716
TI Arabidopsis nonsymbiotic hemoglobin AHb1 modulates nitric oxide bioactivity.
AU Perazzolli Michele; Dominici Paola; Romero-Puertas Maria C; Zago Elisa; Zeier Jurgen; Sonoda Masatoshi; Lamb Chris; Delledonne Massimo
CS Dipartimento Scientifico e Tecnologico, Universita degli Studi di Verona, 37134 Verona, Italy.
SO Plant cell, (2004 Oct) 16 (10) 2785-94.
Journal code: 9208688. ISSN: 1040-4651.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20041007
Last Updated on STN: 20041106
AB **Nitric oxide** (NO) is a widespread signaling molecule, and numerous targets of its action exist in plants. Whereas the activity of NO in erythrocytes, microorganisms, and invertebrates has been shown to be regulated by several hemoglobins, the function of plant hemoglobins in NO detoxification has not yet been elucidated. Here, we show that Arabidopsis thaliana nonsymbiotic hemoglobin AHb1 scavenges NO through production of S-**nitrosohemoglobin** and reduces NO emission under hypoxic stress, indicating its role in NO detoxification. However, AHb1 does not affect NO-mediated hypersensitive cell death in response to avirulent Pseudomonas syringae, suggesting that it is not involved in the removal of NO bursts originated from acute responses when NO mediates crucial defense signaling functions.

L3 ANSWER 2 OF 33 MEDLINE on STN
AN 2004413060 MEDLINE
DN PubMed ID: 15150083
TI Transduction of NO-bioactivity by the red blood cell in sepsis: novel mechanisms of vasodilation during acute inflammatory disease.
AU Crawford Jack H; Chacko Balu K; Pruitt Heather M; Piknova Barbora; Hogg Neil; Patel Rakesh P
CS Department of Pathology, University of Alabama at Birmingham, 901 19th St S, BMR II Rm 307, Birmingham, AL 35294, USA.
NC EB 001980 (NIBIB)
GM 55792 (NIGMS)
HL 70146 (NHLBI)
T32 GM 08361 (NIGMS)
SO Blood, (2004 Sep 1) 104 (5) 1375-82.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200410
ED Entered STN: 20040820
Last Updated on STN: 20041005
Entered Medline: 20041004
AB Sepsis is an acute inflammatory disease characterized by dysfunctional blood flow and hypotension. **Nitric oxide** (NO) is elevated during sepsis and plays an integral role in the associated vascular pathology. However, precise mechanisms and functions of NO in sepsis remain unclear. In this study, we show that red blood cells (RBCs) are foci for nitrosative reactions during acute inflammation, resulting in the formation of cells that can promote systemic vascular relaxation in an uncontrolled manner. Specifically, using experimental models of

endotoxemia and surgical sepsis, NO adducts were found in the RBCs, including S-**nitrosohemoglobin** (SNOHb). These RBCs, referred to as septic RBCs, spontaneously stimulated vasodilation in a manner consistent with elevated SNOHb concentrations. Moreover, relaxation was cyclic guanosine monophosphate (cGMP) dependent and was inhibited by RBC lysis and glutathione but not by the NO scavenger 2-(4-carboxyphenyl)-4,4,5,5 tetramethylimidazoline 1-oxyl 3-oxide (C-PTIO). The potential mechanism of septic RBC-mediated vasorelaxation is discussed and may involve the intermediate, nitroxyl (HNO). Coupled with data showing that NO adducts in septic RBCs were dependent on the inducible **nitric oxide** synthase and correlated with plasma nitrite, these findings provide a novel framework to understand mechanisms underlying dysfunctional blood flow responses during sepsis. Specifically, the concept that RBCs directly mediate systemic hypotension through NO-dependent mechanisms is discussed.

CT Check Tags: Male; Support, U.S. Gov't, P.H.S.
Acute Disease
Animals
Cecum: IN, injuries
Disease Models, Animal
*Erythrocytes: ME, metabolism
Hemoglobins: ME, metabolism
Ligation
Lipopolysaccharides: PD, pharmacology
*Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: ME, metabolism
Nitrites: BL, blood
Oxygen: ME, metabolism
Rats
Rats, Sprague-Dawley
Sepsis: IM, immunology
*Sepsis: ME, metabolism
*Sepsis: PP, physiopathology
*Vasodilation: PH, physiology
Wounds, Stab

RN 10102-43-9 (Nitric Oxide); 7782-44-7 (Oxygen)

CN 0 (Hemoglobins); 0 (Lipopolysaccharides); 0 (Nitrites); 0 (S-nitrosohemoglobin); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L3 ANSWER 3 OF 33 MEDLINE on STN

AN 2004143191 MEDLINE

DN PubMed ID: 15023874

TI Red blood cell nitric oxide as an endocrine vasoregulator: a potential role in congestive heart failure.

AU Datta Borunendra; Tufnell-Barrett Timothy; Bleasdale Robert A; Jones Christopher J H; Beeton Ian; Paul Vincent; Frenneaux Michael; James Philip

CS Department of Cardiology, Wales Heart Research Institute, University of Wales College of Medicine, Heath Park, Cardiff, UK.

SO Circulation, (2004 Mar 23) 109 (11) 1339-42.
Journal code: 0147763. ISSN: 1524-4539.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200407

ED Entered STN: 20040324
Last Updated on STN: 20040709
Entered Medline: 20040708

AB BACKGROUND: A respiratory cycle for **nitric oxide** (NO) would involve the formation of vasoactive metabolites between NO and hemoglobin during pulmonary oxygenation. We investigated the role of

these metabolites in hypoxic tissue in vitro and in vivo in healthy subjects and patients with congestive heart failure (CHF). METHODS AND RESULTS: We investigated the capacity for red blood cells (RBCs) to dilate preconstricted aortic rings under various O2 tensions. RBCs induced cyclic guanylyl monophosphate-dependent vasorelaxation during hypoxia (35+/-4% at 1% O2, 4.7+/-1.6% at 95% O2; P<0.05). RBC-induced relaxations during hypoxia correlated with S-**nitrosohemoglobin** (SNO-Hb) (R2=0.88) but not iron nitrosylhemoglobin (HbFeNO) content. Relaxation responses for RBCs were compared with S-nitrosoglutathione across a range of O2 tensions. The fold increases in relaxation evoked by RBCs were significantly greater at 1% and 2% O2 compared with relaxations induced at 95% (P<0.05), consistent with an allosteric mechanism of hypoxic vasodilation. We also measured transpulmonary gradients of NO metabolites in healthy control subjects and in patients with CHF. In CHF patients but not control subjects, levels of SNO-Hb increase from 0.00293+/-0.00089 to 0.00585+/-0.00137 mol NO/mol hemoglobin tetramer (P=0.005), whereas HbFeNO decreases from 0.00361+/-0.00109 to 0.00081+/-0.00040 mol NO/mol hemoglobin tetramer (P=0.03) as hemoglobin is oxygenated in the pulmonary circulation. These metabolite gradients correlated with the hemoglobin O2 saturation gradient (P<0.05) and inversely with cardiac index (P<0.05) for both CHF patients and control subjects. CONCLUSIONS: We confirm that RBC-bound NO mediates hypoxic vasodilation in vitro. Transpulmonary gradients of hemoglobin-bound NO are evident in CHF patients and are inversely dependent on cardiac index. Hemoglobin may transport and release NO bioactivity to areas of tissue hypoxia or during increased peripheral oxygen extraction via an allosteric mechanism.

CT Check Tags: Female; Human; In Vitro; Male; Support, Non-U.S. Gov't
Allosteric Regulation
Animals
*Anoxia: ME, metabolism
Aorta, Thoracic
Cardiac Output
Cell Hypoxia
*Erythrocytes: ME, metabolism
*Heart Failure, Congestive: BL, blood
Hemoglobins: AN, analysis
Iron: BL, blood
Lung: ME, metabolism
Middle Aged
Nitric Oxide: BL, blood
*Nitric Oxide: PH, physiology
Nitrogen Oxides: BL, blood
Oxygen: BL, blood
Oxygen: PD, pharmacology
Partial Pressure
Rabbits
S-Nitrosoglutathione: BL, blood
Vasodilation

RN 10102-43-9 (Nitric Oxide); 57564-91-7 (S-Nitrosoglutathione); 68586-27-6 (dinitrosyl iron complex); 7439-89-6 (Iron); 7782-44-7 (Oxygen)

CN 0 (Hemoglobins); 0 (Nitrogen Oxides); 0 (S-nitrosohemoglobin)

L3 ANSWER 4 OF 33 MEDLINE on STN

AN 2004190946 MEDLINE

DN PubMed ID: 14963010

TI Vasorelaxation by red blood cells and impairment in diabetes: reduced nitric oxide and oxygen delivery by glycated hemoglobin.

CM Comment in: Circ Res. 2004 Apr 16;94(7):851-5. PubMed ID: 15087423
Comment in: Circ Res. 2004 Jun 25;94(12):e105. PubMed ID: 15217920

AU James Philip E; Lang Derek; Tufnell-Barret Timothy; Milsom Alex B; Frenneaux Michael P

CS Department of Cardiology, Wales Heart Research Institute, University of

Wales College of Medicine, Heath Park, Cardiff, Wales, UK..
Jamespp@Cardiff.ac.uk
SO Circulation research, (2004 Apr 16) 94 (7) 976-83.
Journal code: 0047103. ISSN: 1524-4571.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200408
ED Entered STN: 20040417
Last Updated on STN: 20040824
Entered Medline: 20040823
AB Vascular dysfunction in diabetes is attributed to lack of bioavailable **nitric oxide** (NO) and is postulated as a primary cause of small vessel complications as a result of poor glycemic control. Although it has been proposed that NO is bound by red blood cells (RBCs) and can induce relaxation of blood vessels distal to its site of production in the normal circulation, the effect of RBC glycation on NO binding and relaxation of hypoxic vessels is unknown. We confirm RBC-induced vessel relaxation is inversely related to tissue oxygenation and is proportional to RBC S-**nitrosohemoglobin** (HbSNO) content (but not nitrosylhemoglobin content). We show more total NO bound inside highly glycated RBCs (0.0134 versus 0.0119 NO/Hb, respectively; $P<0.05$) although proportionally less HbSNO (0.0053 versus 0.0088 NO/Hb, respectively; $P<0.05$). We also show glycosylation impairs the vasodilator function of RBCs within a physiological range of tissue oxygenation. These findings may represent an important contribution to reduced NO bioavailability in the microvasculature in diabetes.
CT Check Tags: Comparative Study; Male; Support, Non-U.S. Gov't
Animals
Aorta, Thoracic
Cell Hypoxia
*Diabetes Mellitus: BL, blood
Diabetes Mellitus: PP, physiopathology
Endothelium, Vascular: DE, drug effects
Endothelium, Vascular: ME, metabolism
Erythrocytes: CH, chemistry
*Erythrocytes: PH, physiology
Glycosylation
*Hemoglobin A, Glycosylated: ME, metabolism
*Hemoglobins: ME, metabolism
Microcirculation
*Nitric Oxide: BL, blood
*Oxygen: BL, blood
Phenylephrine: PD, pharmacology
Rabbits
Triazenes: PD, pharmacology
Vasoconstrictor Agents: PD, pharmacology
*Vasodilation: PH, physiology
omega-N-Methylarginine: PD, pharmacology
RN 10102-43-9 (Nitric Oxide); 146724-86-9 (NOC 9); 17035-90-4 (omega-N-Methylarginine); 59-42-7 (Phenylephrine); 7782-44-7 (Oxygen)
CN 0 (Hemoglobin A, Glycosylated); 0 (Hemoglobins); 0 (S-nitrosohemoglobin); 0 (Triazenes); 0 (Vasoconstrictor Agents); 0 (nitrosyl hemoglobin)

L3 ANSWER 5 OF 33 MEDLINE on STN
AN 2004166073 MEDLINE
DN PubMed ID: 15059635
TI S-nitrosohemoglobin: a biochemical perspective.
AU Zhang Yanhong; Hogg Neil
CS Department of Biophysics and Free Radical Research Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA.

NC EB001980 (NIBIB)
GM55792 (NIGMS)
SO Free radical biology & medicine, (2004 Apr 15) 36 (8) 947-58. Ref: 78
Journal code: 8709159. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200411
ED Entered STN: 20040403
Last Updated on STN: 20041109
Entered Medline: 20041108
AB It has been suggested that S-**nitrosohemoglobin** (HbSNO) is an oxygen-dependent mediator of **nitric oxide** delivery to vascular smooth muscle cells, thus regulating vascular tone and blood flow. Central to this much-debated hypothesis is the concept that our previous understanding of the interaction between **nitric oxide** and ferrous hemoglobin was deficient. In this review we will examine the chemical and biochemical mechanisms for the formation of HbSNO, the properties of HbSNO, and the release of **nitric oxide** from HbSNO. This review concludes that although novel reactions of **nitric oxide**, nitrite, and S-nitrosothiols with hemoglobin have been uncovered, there is little evidence to support the notion that the interaction of **nitric oxide** with ferrous hemoglobin is more complex than had been previously established.
CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals
Free Radicals
Heme: CH, chemistry
Hemoglobins: CH, chemistry
*Hemoglobins: PH, physiology
Models, Biological
Models, Chemical
Models, Molecular
Nitric Oxide: CH, chemistry
*Nitric Oxide: ME, metabolism
Nitrites: ME, metabolism
Oxidation-Reduction
Oxygen: CH, chemistry
RN 10102-43-9 (Nitric Oxide); 14875-96-8 (Heme); 7782-44-7 (Oxygen)
CN 0 (Free Radicals); 0 (Hemoglobins); 0 (Nitrites); 0 (S-nitrosohemoglobin)

L3 ANSWER 6 OF 33 MEDLINE on STN
AN 2004269212 MEDLINE
DN PubMed ID: 15165746
TI Nitric oxide, S-nitrosothiols and hemoglobin: is methodology the key?.
AU Giustarini Daniela; Milzani Aldo; Colombo Roberto; Dalle-Donne Isabella; Rossi Ranieri
CS Department of Neuroscience, Pharmacology Section, Via A. Moro 4, University of Siena, 53100 Siena, Italy.
SO Trends in pharmacological sciences, (2004 Jun) 25 (6) 311-6. Ref: 55
Journal code: 7906158. ISSN: 0165-6147.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200407

ED Entered STN: 20040529
Last Updated on STN: 20040723
Entered Medline: 20040722

AB Two main hypotheses describe the role of hemoglobin in the regulation of **nitric oxide** (NO) bioavailability. It has been suggested that hemoglobin interacts with circulating NO, forming Fe-nitrosyl hemoglobin and then S-nitrosothiols, which deliver NO extracellularly by an allosterically regulated mechanism. Alternatively, the existence of diffusional barriers that protect NO from hemoglobin-mediated degradation has been proposed. The reliability of each model in vivo is supported by the detection of physiological hematic levels of S-**nitrosohemoglobin**. However, the measured concentrations of S-**nitrosohemoglobin** are largely divergent between the two models. Moreover, recent reports suggest that circulating levels of S-**nitrosohemoglobin** in human blood could be significantly lower than assessed previously. We suggest that solving the methodological controversies that make the field of NO research a 'minefield', even for skilled analysts, is fundamental to understanding the role of S-nitrosothiols in the vasculature.

CT Check Tags: Human; Support, Non-U.S. Gov't
*Hemoglobins: ME, metabolism
*Nitric Oxide: ME, metabolism
*Nitric Oxide Donors: ME, metabolism
S-Nitrosothiols: BL, blood
*S-Nitrosothiols: ME, metabolism

RN 10102-43-9 (Nitric Oxide)

CN 0 (Hemoglobins); 0 (Nitric Oxide Donors); 0 (S-Nitrosothiols)

L3 ANSWER 7 OF 33 MEDLINE on STN

AN 2004374462 IN-PROCESS

DN PubMed ID: 15275868

TI Bound NO in human red blood cells: fact or artifact?.

AU Bryan Nathan S; Rassaf Tienush; Rodriguez Juan; Feelisch Martin

CS Whitaker Cardiovascular Institute, Boston University School of Medicine, Boston, MA 02118, USA.

NC R01 HL 69029 (NHLBI)

SO Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society, (2004 Jun) 10 (4) 221-8.
Journal code: 9709307. ISSN: 1089-8603.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS IN-PROCESS; NONINDEXED; Priority Journals

ED Entered STN: 20040728
Last Updated on STN: 20040901

AB There has been considerable debate over the nature and chemistry of the interaction between **nitric oxide** (NO) and red blood cells (RBCs), in particular whether hemoglobin consumes or conserves NO bioactivity. Given the vast range of nitrosation levels reported for human RBCs in the literature, we sought to investigate whether there was a common denominator that could account for such discrepancies across different methodologies and reaction conditions and if such a pathway may exist in physiology. Here, we show that there are marked differences in reactivity toward NO between human and rat hemoglobin, which offers a mechanistic explanation for why basal levels of NO-adducts in primate RBCs are considerably lower than those in rodents. We further demonstrate that the inadvertent introduction of trace amounts of nitrite and incomplete thiol alkylation lead to rapid heme and thiol nitros(yl)ation, with generation of nitrosylhemoglobin (NOHb) and S-**nitrosohemoglobin** (SNOHb), while neither species is detectable in human RBCs at physiological nitrite concentrations. Thus, caution should be exercised in interpreting experimental results on SNOHb/NOHb levels that were

obtained in the absence of knowledge about the degree of nitrite contamination, in particular when a physiological role for such species is implicated.

L3 ANSWER 8 OF 33 MEDLINE on STN
AN 2004238209 IN-PROCESS
DN PubMed ID: 15135360
TI Reductive nitrosylation and S-nitrosation of hemoglobin in inhomogeneous nitric oxide solutions.
AU Han Tae H; Fukuto Jon M; Liao James C
CS Department of Chemical Engineering, University of California, Los Angeles, CA 90095, USA.
NC R01 HL65741 (NHLBI)
T32 HL07895 (NHLBI)
SO Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society, (2004 Mar) 10 (2) 74-82.
Journal code: 9709307. ISSN: 1089-8603.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20040512
Last Updated on STN: 20040610
AB Elucidating the reaction of **nitric oxide** (NO) with oxyhemoglobin [HbFe(II)O2] is critical to understanding the metabolic fate of NO in the vasculature. At low concentrations of NO, methemoglobin [HbFe(III)] is the only detectable product from this reaction; however, locally high concentrations of NO have been demonstrated to result in some iron-nitrosylhemoglobin [HbFe(II)NO] and S-**nitrosohemoglobin** (SNO-Hb) formation. Reductive nitrosylation through a HbFe(III) intermediate was proposed as a viable pathway under such conditions. Here, we explore another potential mechanism based on mixed valenced Hb tetramers. The oxidation of one or two heme Fe(II) in the R-state HbFe(II)O2 has been observed to lower the oxygen affinity of the remaining heme groups, thus creating the possibility of oxygen release and NO binding at the heme Fe(II) sites. This mixed valenced hypothesis requires an allosteric transition of the Hb tetramer. Hence, this hypothesis can account for HbFe(II)NO formation, but not SNO-Hb formation. Here, we demonstrate that cyanide attenuated the formation of SNO-Hb by 30-40% when a saturated NO bolus was added to 0.1-1.0 mM HbFe(II)O2 solutions. In addition, HbFe(II)NO formation under such inhomogeneous conditions does not require allostericity. Therefore, we concluded that the mixed valenced theory does not play a major role under these conditions, and reductive nitrosylation accounts for a significant fraction of the HbFe(II)NO formed and approximately 30-40% of SNO-Hb. The remaining SNO-Hb is likely formed from NO oxidation products.

L3 ANSWER 9 OF 33 MEDLINE on STN
AN 2003567459 MEDLINE
DN PubMed ID: 14642399
TI Oxidation and nitrosylation of oxyhemoglobin by S-nitrosoglutathione via nitroxyl anion.
AU Spencer Netanya Y; Patel Neil K; Keszler Agnes; Hogg Neil
CS Department of Biophysics and Free Radical Research Center, Medical College of Wisconsin, Milwaukee, WI 53226, USA.
NC EB001980 (NIBIB)
GM55792 (NIGMS)
SO Free radical biology & medicine, (2003 Dec 1) 35 (11) 1515-26.
Journal code: 8709159. ISSN: 0891-5849.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200407
ED Entered STN: 20031216
Last Updated on STN: 20040703
Entered Medline: 20040702
AB The reaction between low molecular weight S-nitrosothiols and hemoglobin is often used to synthesize S-**nitrosohemoglobin**, a form of hemoglobin suggested to be involved in the regulation of vascular oxygen delivery. However, this reaction has not been studied in detail, and several groups have reported a variable co-formation of oxidized methemoglobin (metHb) during synthesis. This study examines the mechanism of metHb formation and shows that nitrosylhemoglobin (HbNO) can also be formed. Generation of metHb and HbNO is largely dependent on the presence of protein thiol groups. We present evidence for a mechanism for the formation of metHb and HbNO involving the intermediacy of nitroxyl anion. Specifically, the reaction of nitroxyl with S-nitrosothiols to liberate **nitric oxide** and reduced thiol is proposed to be central to the reaction mechanism.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Anions
Copper: CH, chemistry
Cysteine: CH, chemistry
Electrodes
Electron Spin Resonance Spectroscopy
Hemoglobins: CH, chemistry
Hydrogen-Ion Concentration
Kinetics
Models, Chemical
Nitric Oxide: CH, chemistry
Nitrogen: CH, chemistry
*Nitrogen: ME, metabolism
*Nitrogen Oxides
*Oxygen: ME, metabolism
Oxygen Consumption
*Oxyhemoglobins: CH, chemistry
*S-Nitrosoglutathione: CH, chemistry
S-Nitrosothiols: CH, chemistry
Time Factors
RN 10102-43-9 (Nitric Oxide); 14332-28-6 (nitroxyl); 52-90-4 (Cysteine); 57564-91-7 (S-Nitrosoglutathione); 7440-50-8 (Copper); 7727-37-9 (Nitrogen); 7782-44-7 (Oxygen)
CN 0 (Anions); 0 (Hemoglobins); 0 (Nitrogen Oxides); 0 (Oxyhemoglobins); 0 (S-Nitrosothiols); 0 (S-nitrosohemoglobin); 0 (nitrosyl hemoglobin)

L3 ANSWER 10 OF 33 MEDLINE on STN
AN 2003102130 MEDLINE
DN PubMed ID: 12615064
TI Effect of nitric oxide on the transport and release of oxygen in fetal blood.
AU Clementi Maria Elisabetta; Orsini Federica; Schinina Maria Eugenia; Noia Giuseppe; Giardina Bruno
CS CNR Institute Chimica del riconoscimento Molecolare, Catholic University, Largo F. Vito 1, 00168 Rome, Italy.. e.clementi@uniserv.ccr.rm.cnr.it
SO Biochemical and biophysical research communications, (2003 Mar 14) 302 (3) 515-9.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200305

ED Entered STN: 20030305
Last Updated on STN: 20030514
Entered Medline: 20030513

AB It is well known that **nitric oxide** (NO), the most important vasodilator agent, plays an important role in lowering vascular resistance in the human umbilical-placental circulation and that its deficiency is related to the pathogenesis of pre-eclamptic disorder. Besides it has recently been demonstrated that human hemoglobin (HbA) is able to transport **nitric oxide**, as S-**nitrosohemoglobin** (SNO-Hb), from the arterial to the venous blood. In the present study we examine the functional properties of the adult and fetal nitrosated hemoglobins to see if the double transport of oxygen and NO may influence the fetal oxygenation and the relation between maternal and fetal blood. Our results show that S-nitrosation significantly increases the oxygen affinity of the adult Hb (HbA) with respect to native protein (no-nitrosated) while the functional properties of HbF are less influenced. The oxygen affinity modification, found for SNO-HbA, was ascribed to the nitrosation of cysteine beta 93: really, the same residue is also present in the gamma chains of fetal hemoglobin, while the increase of affinity is less evidenced; hence, it is probable that the 39 aminoacidic substitutions between beta and gamma chains allay the effects of S-nitrosation. As regards the physiological modulators (protons, chloride ions, 2,3-diphosphoglyceric acid, and temperature), they influence the oxygen affinity of the two hemoglobins S-nitrosated, in equal mode with respect to the native forms determining the same variation on the oxygen affinity. Hence, our results evidence the fact that the NO release by SNO-HbA "in vivo" would be limited to regions of extremely low oxygen tension (such as hypoxic regions), while in fetus, SNO-HbF would unload **nitric oxide** and oxygen at pressure values close to normal.

CT Check Tags: Human
*Blood: ME, metabolism
*Fetal Hemoglobin: ME, metabolism
Hemoglobin A: ME, metabolism
Hemoglobins: CH, chemistry
Hemoglobins: ME, metabolism
Models, Biological
Models, Molecular
*Nitric Oxide: PD, pharmacology
Nitrogen: ME, metabolism
*Oxygen: ME, metabolism
Pressure
Temperature
Umbilical Cord: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 7727-37-9 (Nitrogen); 7782-44-7 (Oxygen); 9034-51-9 (Hemoglobin A); 9034-63-3 (Fetal Hemoglobin)

CN 0 (Hemoglobins); 0 (S-nitrosohemoglobin)

L3 ANSWER 11 OF 33 MEDLINE on STN

AN 2003233121 MEDLINE

DN PubMed ID: 12754789

TI [The involvement of nitric oxide in formation of hemoglobin oxygen-binding properties].
Uchastie oksida azota v formirovanii kislorodsviazyvaiushchikh svoistv gemoglobina.

AU Zinchuk V V

CS Grodno Medical University, Belarus.

SO Uspekhi fiziologicheskikh nauk, (2003 Apr-Jun) 34 (2) 33-45. Ref: 87
Journal code: 0310750. ISSN: 0301-1798.

CY Russia: Russian Federation

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, TUTORIAL)
LA Russian
FS Priority Journals
EM 200307
ED Entered STN: 20030521
Last Updated on STN: 20030703
Entered Medline: 20030702
AB The analysis of literature and results of our investigations indicate the possible involvement of L-arginine-**nitric oxide** (NO) system in formation of blood oxygen-carrying capacity. In reaction with hemoglobin NO forms methemoglobin, nitrosyl-hemoglobin (HbFe2+NO) and S-**nitrosohemoglobin** (SNO-Hb). The NO-hemoglobin derivatives have the various biological functions (NO transport, storage, elimination etc.) and are involved in the genesis of different pathologic conditions. The presence of different NO-hemoglobin derivatives can differently influence on the whole blood hemoglobin-oxygen affinity (HOA): methemoglobin and SNO-Hb increases, and HbFe2+NO decreases it. Their effect on the blood oxygen-binding properties may be important for the gas exchange processes. At the level of lung capillaries such effect may be the additional mechanism promoting a blood oxygenation, and in the systemic microcirculation it may optimize blood desaturation and hence the tissue oxygen delivery. Blood oxygen-binding properties affect the state of L-arginine-NO system, however this system also may determine HOA through the intraerythrocytic regulatory mechanisms, oxygen-dependent nature of NO generation, regulation of vascular tone and effect of peroxynitrite.
CT Animals
Arginine: ME, metabolism
English Abstract
*Erythrocytes: ME, metabolism
Hemoglobins: CH, chemistry
*Hemoglobins: ME, metabolism
Hemoglobins: PH, physiology
Lung: BS, blood supply
Methemoglobin: PH, physiology
Nitric Oxide: CH, chemistry
*Nitric Oxide: ME, metabolism
Oxygen: CH, chemistry
*Oxygen: ME, metabolism
Oxyhemoglobins: ME, metabolism
Protein Binding
RN 10102-43-9 (Nitric Oxide); 74-79-3 (Arginine); 7782-44-7 (Oxygen); 9008-37-1 (Methemoglobin)
CN 0 (Hemoglobins); 0 (Oxyhemoglobins); 0 (S-nitrosohemoglobin); 0 (nitrosyl hemoglobin)

L3 ANSWER 12 OF 33 MEDLINE on STN
AN 2002127190 MEDLINE
DN PubMed ID: 11841242
TI Iron nitrosyl hemoglobin formation from the reactions of hemoglobin and hydroxyurea.
AU Huang Jinming; Hadimani Shreeshailkumar B; Rupon Jeremy W; Ballas Samir K; Kim-Shapiro Daniel B; King S Bruce
CS Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109, USA.
NC HL62198 (NHLBI)
SO Biochemistry, (2002 Feb 19) 41 (7) 2466-74.
Journal code: 0370623. ISSN: 0006-2960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200203

ED Entered STN: 20020227
Last Updated on STN: 20020403
Entered Medline: 20020327

AB Hydroxyurea represents an approved treatment for sickle cell anemia and acts as a **nitric oxide** donor under oxidative conditions in vitro. Electron paramagnetic resonance spectroscopy shows that hydroxyurea reacts with oxy-, deoxy-, and methemoglobin to produce 2-6% of iron nitrosyl hemoglobin. No S-**nitrosohemoglobin** forms during these reactions. Cyanide and carbon monoxide trapping studies reveal that hydroxyurea oxidizes deoxyhemoglobin to methemoglobin and reduces methemoglobin to deoxyhemoglobin. Similar experiments reveal that iron nitrosyl hemoglobin formation specifically occurs during the reaction of hydroxyurea and methemoglobin. Experiments with hydroxyurea analogues indicate that **nitric oxide** transfer requires an unsubstituted acylhydroxylamine group and that the reactions of hydroxyurea and deoxy- and methemoglobin likely proceed by inner-sphere mechanisms. The formation of nitrate during the reaction of hydroxyurea and oxyhemoglobin and the lack of nitrous oxide production in these reactions suggest the intermediacy of **nitric oxide** as opposed to its redox form nitroxyl. A mechanistic model that includes a redox cycle between deoxyhemoglobin and methemoglobin has been forwarded to explain these results that define the reactivity of hydroxyurea and hemoglobin. These direct **nitric oxide** producing reactions of hydroxyurea and hemoglobin may contribute to the overall pathophysiological properties of this drug.

CT Check Tags: Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Electron Spin Resonance Spectroscopy
Hemoglobin A: CH, chemistry
*Hemoglobins: CH, chemistry
Hemoglobins: ME, metabolism
Hydroxyurea: BL, blood
*Hydroxyurea: CH, chemistry
Iron: BL, blood
*Iron: CH, chemistry
Methemoglobin: CH, chemistry
Models, Chemical
Nitric Oxide: BL, blood
*Nitric Oxide: CH, chemistry
Nitrogen Oxides: BL, blood
*Nitrogen Oxides: CH, chemistry
Oxyhemoglobins: CH, chemistry
Spectrophotometry

RN 10102-43-9 (Nitric Oxide); 127-07-1 (Hydroxyurea); 68586-27-6 (dinitrosyl iron complex); 7439-89-6 (Iron); 9008-02-0 (deoxyhemoglobin); 9008-37-1 (Methemoglobin); 9034-51-9 (Hemoglobin A); 9062-91-3 (oxyhemoglobin A)

CN 0 (Hemoglobins); 0 (Nitrogen Oxides); 0 (Oxyhemoglobins)

L3 ANSWER 13 OF 33 MEDLINE on STN

AN 2002335582 MEDLINE

DN PubMed ID: 12076970

TI Nitric oxide transport and storage in the cardiovascular system.

AU Muller Bernard; Kleschyov Andrei L; Alencar Jacicarlos L; Vanin Anatoly; Stoclet Jean-Claude

CS Universite Louis Pasteur, CNRS UMR 7034, Faculte de Pharmacie, BP 24, 67401 ILLKIRCH Cedex, France.. bmuller@pharma.u-strasbg.fr

SO Annals of the New York Academy of Sciences, (2002 May) 962 131-9. Ref: 38
Journal code: 7506858. ISSN: 0077-8923.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English
FS Priority Journals
EM 200207
ED Entered STN: 20020625
Last Updated on STN: 20020727
Entered Medline: 20020726
AB Despite short halflife in biological fluids, **nitric oxide** (NO) can produce remote or long lasting effect in the cardiovascular system. Long distance transport or local storage of NO might explain these effects. In blood, recent findings suggest that in addition to being a major consumption pathway, interaction of NO with hemoglobin may permit O(2)-governed transport of NO (as S-**nitrosohemoglobin**) to tissues in which NO may be released together with O(2), via transnitrosation of a transport protein. In blood vessels, two different putative NO stores have been characterized. The first is the photosensitive store, formed from endothelium-derived NO. The mechanism of NO release from this store in the body (in absence of light) and its physiological relevance are unknown. The second store is generated in conditions of high tissue NO levels, as a consequence of the inducible NO synthase activity or in various stress conditions. This NO store involves formation of protein-bound dinitrosyl iron complexes or S-nitrosated proteins, or both. Low molecular weight thiols can displace NO from these stores and probably transfer it to target membrane protein(s) such as K(+) channels, via transnitrosation reactions. These stores may be involved in defence mechanisms against inflammation or stress. Thus, NO transport and storage mechanisms may be implicated in a variety of NO effects. The mechanisms of their formation and of NO release and their physiologic and pathophysiologic relevance deserve further investigations.
CT Check Tags: Support, Non-U.S. Gov't
Animals
Biological Transport: PH, physiology
Blood Vessels: CY, cytology
Blood Vessels: ME, metabolism
*Cardiovascular System: ME, metabolism
Erythrocytes: ME, metabolism
Nitric Oxide: BL, blood
*Nitric Oxide: ME, metabolism
Nitric-Oxide Synthase: ME, metabolism
Sulfhydryl Compounds: ME, metabolism
RN 10102-43-9 (Nitric Oxide)
CN 0 (Sulfhydryl Compounds); EC 1.14.13.- (endothelial constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L3 ANSWER 14 OF 33 MEDLINE on STN
AN 2002123418 MEDLINE
DN PubMed ID: 11829532
TI Blood oxygen transport in rats under hypothermia combined with modification of the L-Arginine-NO pathway.
AU Zinchuk V V; Dorokhina L V
CS Department of Physiology, Grodno Medical University, 80 Gorki Street, 230015, Grodno, Belarus.. zinchuk@grsmi.unibel.by
SO Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society, (2002 Feb) 6 (1) 29-34.
Journal code: 9709307. ISSN: 1089-8603.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200304
ED Entered STN: 20020223
Last Updated on STN: 20030404

Entered Medline: 20030403

AB **Nitric oxide** (NO) has high affinity to heme and by interaction with oxyhemoglobin (HbO2) is converted into nitrate to form methemoglobin (MetHb) as a side product. In combining with deoxy-Hb NO yields a stable molecule of nitrosyl-hemoglobin (HbFe(II)NO) that can further be converted into nitrate and hemoglobin (Hb). In addition, Hb was shown to transport NO in a form of S-**nitrosohemoglobin** (SNO-Hb). These features of the Hb and NO interaction are important for blood oxygen transport including hemoglobin-oxygen affinity (HOA). The present investigation was aimed to study the blood oxygen transport indices (pO2, pCO2, pH, HOA, etc.) in rats under hypothermia combined with a modification of L-arginine-NO pathway. To modify the L-arginine-NO pathway, rats were administered with N(G)-nitro-L-arginine methyl ester (L-NAME), L-arginine, or sodium nitroprusside (SNP) intravenously before cooling. A substantial impairment of oxygen delivery and development of hypoxia, with an important contribution of HOA into the latter accompanied the deep hypothermia in rats. All the experimental groups developed metabolic acidosis, less pronounced in rats treated with L-arginine only. In the experiments with a modification of the L-arginine-NO pathway, an enhanced cold resistance, attenuated oxygen deficiency, and a weaker oxyhemoglobin dissociation curve (ODC) shift leftwards were observed only after the administration of L-arginine. Neither SNP nor L-NAME had not any protective effects. L-Arginine lowered the value of standard P50 (pO2, corresponding to 50% Hb saturation with oxygen at 37 degrees C, pH 7.4, and pCO2 = 40 mmHg). The actual P50 (at actual pH, pCO2 and temperature) decreased by approximately 15 mmHg and was significantly higher than that under hypothermia without the drug treatment (21.03 +/- 0.35 vs 17.45 +/- 0.60 mmHg). NO also can contribute to this system through different mechanisms (HOA modification, vascular tone regulation, peroxynitrite formation, and effects).

CT Check Tags: Male; Support, Non-U.S. Gov't
Animals
Arginine: ME, metabolism
Biological Transport: DE, drug effects
Blood Gas Analysis
*Hypothermia: BL, blood
Methemoglobin: DE, drug effects
Methemoglobin: ME, metabolism
Models, Animal
Nitric Oxide: ME, metabolism
*Nitric Oxide: PD, pharmacology
*Oxygen: BL, blood
Oxyhemoglobins: DE, drug effects
Oxyhemoglobins: ME, metabolism
Rats

RN 10102-43-9 (Nitric Oxide); 74-79-3 (Arginine); 7782-44-7 (Oxygen); 9008-37-1 (Methemoglobin)

CN 0 (Oxyhemoglobins)

L3 ANSWER 15 OF 33 MEDLINE on STN DUPLICATE 1

AN 2001404722 MEDLINE

DN PubMed ID: 11457254

TI Release of **nitric oxide** from S-**nitrosohemoglobin**. Electron transfer as a response to deoxygenation.

AU Pezacki J P; Ship N J; Kluger R

CS The Davenport Laboratories, Department of Chemistry, University of Toronto, 80 St. George St., Toronto, Ontario M5S 3H6, Canada.

SO Journal of the American Chemical Society, (2001 May 16) 123 (19) 4615-6. Journal code: 7503056. ISSN: 0002-7863.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS Priority Journals
EM 200109
ED Entered STN: 20010910
Last Updated on STN: 20010910
Entered Medline: 20010906
CT Check Tags: Support, Non-U.S. Gov't
Electron Transport
Heme: CH, chemistry
*Hemoglobins: CH, chemistry
Iron: CH, chemistry
Magnetic Resonance Spectroscopy
*Nitric Oxide: CH, chemistry
*Oxygen: CH, chemistry
RN 10102-43-9 (Nitric Oxide); 14875-96-8 (Heme); 7439-89-6 (Iron); 7782-44-7 (Oxygen)
CN 0 (Hemoglobins); 0 (S-nitrosohemoglobin)

L3 ANSWER 16 OF 33 MEDLINE on STN
AN 2001418860 MEDLINE
DN PubMed ID: 11457881
TI Effects of inhaled nitric oxide on regional blood flow are consistent with intravascular nitric oxide delivery.
AU Cannon R O 3rd; Schechter A N; Panza J A; Ognibene F P; Pease-Fye M E; Waclawiw M A; Shelhamer J H; Gladwin M T
CS Cardiology Branch, National Heart, Lung, and Blood Institute, NIH, Bethesda, Maryland 20892-1650, USA.. cannonr@nih.gov
SO Journal of clinical investigation, (2001 Jul) 108 (2) 279-87.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200108
ED Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816
AB **Nitric oxide** (NO) may be stabilized by binding to hemoglobin, by nitrosating thiol-containing plasma molecules, or by conversion to nitrite, all reactions potentially preserving its bioactivity in blood. Here we examined the contribution of blood-transported NO to regional vascular tone in humans before and during NO inhalation. While breathing room air and then room air with NO at 80 parts per million, forearm blood flow was measured in 16 subjects at rest and after blockade of forearm NO synthesis with N(G)-monomethyl-L-arginine (L-NMMA) followed by forearm exercise stress. L-NMMA reduced blood flow by 25% and increased resistance by 50%, an effect that was blocked by NO inhalation. With NO inhalation, resistance was significantly lower during L-NMMA infusion, both at rest and during repetitive hand-grip exercise. S-**nitrosohemoglobin** and plasma S-nitrosothiols did not change with NO inhalation. Arterial nitrite levels increased by 11% and arterial nitrosyl(heme)hemoglobin levels increased tenfold to the micromolar range, and both measures were consistently higher in the arterial than in venous blood. S-**nitrosohemoglobin** levels were in the nanomolar range, with no significant artery-to-vein gradients. These results indicate that inhaled NO during blockade of regional NO synthesis can supply intravascular NO to maintain normal vascular function. This effect may have application for the treatment of diseases characterized by endothelial dysfunction.
CT Check Tags: Female; Human; Male
Administration, Inhalation

Adult
Biological Transport
Endothelium, Vascular: ME, metabolism
Forearm
Hemoglobins: AN, analysis
*Mercaptoethanol
Middle Aged
Models, Chemical
Nitric Oxide: AD, administration & dosage
Nitric Oxide: BL, blood
*Nitric Oxide: PD, pharmacology
Nitrites: BL, blood
Nitroso Compounds: BL, blood
*Regional Blood Flow: DE, drug effects
*S-Nitrosothiols
RN 10102-43-9 (Nitric Oxide); 60-24-2 (Mercaptoethanol); 67616-44-8 (S-nitrosomercaptoethanol)
CN 0 (Hemoglobins); 0 (Nitrites); 0 (Nitroso Compounds); 0 (S-Nitrosothiols); 0 (S-nitrosohemoglobin); 0 (nitrosyl hemoglobin)

L3 ANSWER 17 OF 33 MEDLINE on STN
AN 2001644568 MEDLINE
DN PubMed ID: 11697198
TI Nitric oxide transport on sickle cell hemoglobin: where does it bind?.
AU Gladwin M T; Ognibene F P; Shelhamer J H; Pease-Fye M E; Noguchi C T; Rodgers G P; Schechter A N
CS Critical Care Medicine Department, Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA.. mgladwin@nih.gov
SO Free radical research, (2001 Aug) 35 (2) 175-80.
Journal code: 9423872. ISSN: 1071-5762.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20011108
Last Updated on STN: 20020213
Entered Medline: 20020212
AB We have recently reported that **nitric oxide** inhalation in individuals with sickle cell anemia increases the level of NO bound to hemoglobin, with the development of an arterial-venous gradient, suggesting delivery to the tissues. A recent model suggests that **nitric oxide**, in addition to its well-known reaction with heme groups, reacts with the beta-globin chain cysteine 93 to form S-**nitrosohemoglobin** (SNO-Hb) and that SNO-Hb would preferentially release **nitric oxide** in the tissues and thus modulate blood flow. However, we have also recently determined that the primary NO hemoglobin adduct formed during NO breathing in normal (hemoglobin A) individuals is nitrosyl (heme)hemoglobin (HbFeIINO), with only a small amount of SNO-Hb formation. To determine whether the NO is transported as HbFeIINO or SNO-Hb in sickle cell individuals, which would have very different effects on sickle hemoglobin polymerization, we measured these two hemoglobin species in three sickle cell volunteers before and during a dose escalation of inhaled NO (40, 60, and 80 ppm). Similar to our previous observations in normal individuals, the predominant species formed was HbFeIINO, with a significant arterial-venous gradient. Minimal SNO-Hb was formed during NO breathing, a finding inconsistent with significant transport of NO using this pathway, but suggesting that this pathway exists. These results suggest that NO binding to heme groups is physiologically a rapidly reversible process, supporting a revised model of hemoglobin delivery of NO in the peripheral circulation and consistent with the possibility that NO delivery by hemoglobin may be therapeutically

useful in sickle cell disease.
CT Check Tags: Human
*Anemia, Sickle Cell: ME, metabolism
*Anemia, Sickle Cell: PA, pathology
Binding Sites
Biological Transport
Chemiluminescence
Dose-Response Relationship, Drug
Erythrocytes: DE, drug effects
Erythrocytes: ME, metabolism
*Hemoglobin, Sickle: ME, metabolism
Hemoglobins: ME, metabolism
*Nitric Oxide: ME, metabolism
Nitric Oxide: PD, pharmacology
Protein Binding
RN 10102-43-9 (Nitric Oxide)
CN 0 (Hemoglobin, Sickle); 0 (Hemoglobins); 0 (S-nitrosohemoglobin); 0 (nitrosyl hemoglobin)

L3 ANSWER 18 OF 33 MEDLINE on STN
AN 2001082661 MEDLINE
DN PubMed ID: 10945989
TI Reaction of S-nitrosoglutathione with the heme group of deoxyhemoglobin.
AU Spencer N Y; Zeng H; Patel R P; Hogg N
CS Biophysics Research Institute and Free Radical Research Center, Medical College of Wisconsin, Milwaukee, Wisconsin 53226, USA.
NC GM 55792 (NIGMS)
RR 01008 (NCRR)
SO Journal of biological chemistry, (2000 Nov 24) 275 (47) 36562-7.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010108
AB The mechanism of interaction between S-nitrosoglutathione (GSNO) and hemoglobin is a crucial component of hypotheses concerning the role played by S-**nitrosohemoglobin** in vivo. We previously demonstrated (Patel, R. P., Hogg, N., Spencer, N. Y., Kalyanaraman, B., Matalon, S., and Darley-Usmar, V. M. (1999) J. Biol. Chemical 274, 15487-15492) that transnitrosation between oxygenated hemoglobin and GSNO is a slow, reversible process, and that the reaction between GSNO and deoxygenated hemoglobin (deoxyHb) did not conform to second order reversible kinetics. In this study we have reinvestigated this reaction and show that GSNO reacts with deoxyHb to form glutathione, **nitric oxide**, and ferric hemoglobin. **Nitric oxide** formed from this reaction is immediately autocaptured to form nitrosylated hemoglobin. GSNO reduction by deoxyHb is essentially irreversible. The kinetics of this reaction depended upon the conformation of the protein, with more rapid kinetics occurring in the high oxygen affinity state (i.e. modification of the Cysbeta-93) than in the low oxygen affinity state (i.e. treatment with inositol hexaphosphate). A more rapid reaction occurred when deoxymyoglobin was used, further supporting the observation that the kinetics of reduction are directly proportional to oxygen affinity. This observation provides a mechanism for how deoxygenation of hemoglobin/myoglobin could facilitate **nitric oxide** release from S-nitrosothiols and represents a potential physiological mechanism of S-nitrosothiol metabolism.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.

Cell Line
Chemiluminescence
Chromatography, High Pressure Liquid
Electron Spin Resonance Spectroscopy
Ethylmaleimide: ME, metabolism
*Glutathione: AA, analogs & derivatives
Glutathione: ME, metabolism
*Heme: ME, metabolism
*Hemoglobins: ME, metabolism
Nitric Oxide: ME, metabolism
*Nitroso Compounds: ME, metabolism
Pentetic Acid: ME, metabolism
S-Nitrosoglutathione
Ultrafiltration

RN 10102-43-9 (Nitric Oxide); 128-53-0 (Ethylmaleimide); 14875-96-8 (Heme); 57564-91-7 (S-Nitrosoglutathione); 67-43-6 (Pentetic Acid); 70-18-8 (Glutathione); 9008-02-0 (deoxyhemoglobin)

CN 0 (Hemoglobins); 0 (Nitroso Compounds)

L3 ANSWER 19 OF 33 MEDLINE on STN

AN 2001022674 MEDLINE

DN PubMed ID: 11027349

TI Role of circulating nitrite and S-nitrosohemoglobin in the regulation of regional blood flow in humans.

AU Gladwin M T; Shelhamer J H; Schechter A N; Pease-Fye M E; Waclawiw M A; Panza J A; Ognibene F P; Cannon R O 3rd

CS Critical Care Medicine Department of the Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA.. mgladwin@mail.cc.nih.gov

SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Oct 10) 97 (21) 11482-7.
Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200011

ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001109

AB To determine the relative contributions of endothelial-derived **nitric oxide** (NO) vs. intravascular nitrogen oxide species in the regulation of human blood flow, we simultaneously measured forearm blood flow and arterial and venous levels of plasma nitrite, LMW-SNOs and HMW-SNOs, and red cell S-**nitrosohemoglobin** (SNO-Hb). Measurements were made at rest and during regional inhibition of NO synthesis, followed by forearm exercise. Surprisingly, we found significant circulating arterial-venous plasma nitrite gradients, providing a novel delivery source for intravascular NO. Further supporting the notion that circulating nitrite is bioactive, the consumption of nitrite increased significantly with exercise during the inhibition of regional endothelial synthesis of NO. The role of circulating S-nitrosothiols and SNO-Hb in the regulation of basal vascular tone is less certain. We found that low-molecular-weight S-nitrosothiols were undetectable and S-nitroso-albumin levels were two logs lower than previously reported. In fact, S-nitroso-albumin primarily formed in the venous circulation, even during NO synthase inhibition. Whereas SNO-Hb was measurable in the human circulation (brachial artery levels of 170 nM in whole blood), arterial-venous gradients were not significant, and delivery of NO from SNO-Hb was minimal. In conclusion, we present data that suggest (i) circulating nitrite is bioactive and provides a delivery gradient of intravascular NO, (ii) S-nitroso-albumin does not deliver NO

from the lungs to the tissue but forms in the peripheral circulation, and (iii) SNO-Hb and S-nitrosothiols play a minimal role in the regulation of basal vascular tone, even during exercise stress.

CT Check Tags: Female; Human; Male
Adult
*Hemoglobins: PH, physiology
Middle Aged
Nitrates: BL, blood
Nitric Oxide: BL, blood
*Nitric Oxide: PH, physiology
Nitric-Oxide Synthase: AI, antagonists & inhibitors
Nitric-Oxide Synthase: ME, metabolism
Regional Blood Flow: PH, physiology

RN 10102-43-9 (Nitric Oxide)

CN 0 (Hemoglobins); 0 (Nitrates); 0 (S-nitrosohemoglobin); EC 1.14.13.- (endothelial constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L3 ANSWER 20 OF 33 MEDLINE on STN

AN 2000474432 MEDLINE

DN PubMed ID: 10954746

TI Relative role of heme nitrosylation and beta-cysteine 93 nitrosation in the transport and metabolism of nitric oxide by hemoglobin in the human circulation.

AU Gladwin M T; Ognibene F P; Pannell L K; Nichols J S; Pease-Fye M E; Shelhamer J H; Schechter A N

CS Critical Care Medicine Department of the Warren G. Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA.. mgladwin@nih.gov

SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Aug 29) 97 (18) 9943-8.
Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200010

ED Entered STN: 20001012
Last Updated on STN: 20001012
Entered Medline: 20001005

AB To quantify the reactions of **nitric oxide** (NO) with hemoglobin under physiological conditions and to test models of NO transport on hemoglobin, we have developed an assay to measure NO-hemoglobin reaction products in normal volunteers, under basal conditions and during NO inhalation. NO inhalation markedly raised total nitrosylated hemoglobin levels, with a significant arterial-venous gradient, supporting a role for hemoglobin in the transport and delivery of NO. The predominant species accounting for this arterial-venous gradient is nitrosyl(heme)hemoglobin. NO breathing increases S-nitrosation of hemoglobin beta-chain cysteine 93, however only to a fraction of the level of nitrosyl(heme)hemoglobin and without a detectable arterial-venous gradient. A strong correlation between methemoglobin and plasma nitrate formation was observed, suggesting that NO metabolism is a primary physiological cause of hemoglobin oxidation. Our results demonstrate that NO-heme reaction pathways predominate in vivo, NO binding to heme groups is a rapidly reversible process, and S-**nitrosohemoglobin** formation is probably not a primary transport mechanism for NO but may facilitate NO release from heme.

CT Check Tags: Human
Administration, Inhalation
Chemiluminescence
*Cysteine

*Heme: CH, chemistry
Heme: ME, metabolism
*Hemoglobins: CH, chemistry
*Hemoglobins: ME, metabolism
Kinetics
Nitrates: BL, blood
Nitric Oxide: AD, administration & dosage
*Nitric Oxide: BL, blood
Nitric Oxide: PK, pharmacokinetics
Nitrites: BL, blood
*Nitroso Compounds: BL, blood
Ozone
Potassium Cyanide: PK, pharmacokinetics
Reproducibility of Results
Sensitivity and Specificity

RN 10028-15-6 (Ozone); 10102-43-9 (Nitric Oxide); 14875-96-8 (Heme); 151-50-8 (Potassium Cyanide); 52-90-4 (Cysteine)

CN 0 (Hemoglobins); 0 (Nitrates); 0 (Nitrites); 0 (Nitroso Compounds)

L3 ANSWER 21 OF 33 MEDLINE on STN

AN 2001125353 MEDLINE

DN PubMed ID: 11139362

TI Determination of S-nitrosohemoglobin using a solid-state amperometric sensor.

AU Palmerini C A; Arienti G; Palombari R

CS Dipartimento di Biologia Cellulare e Molecolare, Universita di Perugia, Via del Giochetto, Perugia 06127, Italy.. arienti@unipg.it

SO Nitric oxide : biology and chemistry / official journal of the Nitric Oxide Society, (2000 Dec) 4 (6) 546-9.
Journal code: 9709307. ISSN: 1089-8603.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200102

ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB **Nitric oxide** (NO, nitrogen monoxide), generated in biological systems, plays important roles as a regulatory molecule. Its ability to bind to hemoglobin (Hb) iron is well known. Moreover, it may lose an electron, forming the nitrosonium ion, involved in the synthesis of nitrosothiols (RSNO). It has been suggested that S-**nitrosohemoglobin** (SNO-Hb) may act as a reservoir of NO. The S-nitrosylation of Hb can be detected after the incubation of CysNO and Hb for 60 min with a molecular ratio (CysNO/hem) of 1:1. Upon increasing the ratio to 10:1, about 50% of total Hb (100% of beta-chain -SH 93) was derivatized in 60 min. In this paper, we describe a new method for the quantitative assay of SNO-Hb, after the liberation of NO by Cu(2+)/Cu(+) and the simultaneous assessment of NO by solid-state amperometric sensor. The assay described by us is sensitive, rapid, easy to perform, and inexpensive. For this reason, we believe that it may represent an important analytical improvement for the study of the S-transnitrosylation reactions between RSNO and the Hb Cys-beta 93 and SNO-Hb and glutathione.

CT *Biosensing Techniques: IS, instrumentation
Calibration
*Cysteine: AA, analogs & derivatives
Cysteine: CH, chemistry
Electrochemistry: EC, economics
*Electrochemistry: IS, instrumentation
Electrochemistry: MT, methods

*Hemoglobins: AN, analysis
Hemoglobins: CH, chemistry
Nitric Oxide: CH, chemistry
Nitroso Compounds: CH, chemistry
Reproducibility of Results
*S-Nitrosothiols
Sensitivity and Specificity
Time Factors

RN 10102-43-9 (Nitric Oxide); 51209-75-7 (S-nitrosocysteine); 52-90-4 (Cysteine)

CN 0 (Hemoglobins); 0 (Nitroso Compounds); 0 (S-Nitrosothiols); 0 (S-nitrosohemoglobin)

L3 ANSWER 22 OF 33 MEDLINE on STN

AN 2000164551 MEDLINE

DN PubMed ID: 10699753

TI Dynamic state of S-nitrosothiols in human plasma and whole blood.

AU Jourd'heuil D; Hallen K; Feelisch M; Grisham M B

CS Vascular Biology Research Group, Albany Medical College, Albany, NY 12208, USA.. david-jourd'heuil@ccgateway.amc.edu

NC DK43785 (NIDDK)
DK47663 (NIDDK)

SO Free radical biology & medicine, (2000 Feb 1) 28 (3) 409-17.
Journal code: 8709159. ISSN: 0891-5849.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200004

ED Entered STN: 20000421
Last Updated on STN: 20000421
Entered Medline: 20000411

AB In the vasculature, nitrosothiols derived from the **nitric oxide** (NO)-mediated S-nitrosation of thiols play an important role in the transport, storage, and metabolism of NO. The present study was designed to examine the reactions that promote the decomposition, formation, and distribution of extracellular nitrosothiols in the circulation. The disappearance of these species in plasma and whole blood was examined using a high-performance liquid chromatography method to separate low- and high-molecular weight nitrosothiols. We found that incubation of S-nitrosocysteine (CySNO) or S-nitrosoglutathione (GSNO) with human plasma resulted in a rapid decomposition of these nitrosothiols such that <10% of the initial concentration was recovered after 10-15 min. Neither metal chelators (DTPA, neocuproine), nor zinc chloride (glutathione peroxidase inhibitor), acivicin (gamma-glutamyl transpeptidase inhibitor), or allopurinol (xanthine oxidase inhibitor) inhibited the decomposition of GSNO. With both CySNO and GSNO virtually all NO was recovered as S-nitrosoalbumin (AlbSNO), suggesting the involvement of a direct transnitrosation reaction. Electrophilic attack of the albumin-associated thiols by reactive nitrogen oxides formed from the interaction of NO with O(2) was ruled out because one would have expected 50% yield of AlbSNO. Similar results were obtained in whole blood. The amount of S-**nitrosohemoglobin** recovered in the presence of 10 microM GSNO or CySNO was less than 100 nM taking into consideration the detection limit of the assay used. Our results suggest that serum albumin may act as a sink for low-molecular-weight nitrosothiols and as a modulator of NO(+) transfer between the vascular wall and intraerythrocytic hemoglobin.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
Allopurinol: PD, pharmacology
Biotransformation
Chelating Agents: PD, pharmacology

Chlorides: PD, pharmacology
Chromatography, High Pressure Liquid
Cysteine: AA, analogs & derivatives
Cysteine: BL, blood
Enzyme Inhibitors: PD, pharmacology
Glutathione: AA, analogs & derivatives
Glutathione: BL, blood
Isoxazoles: PD, pharmacology
*Mercaptoethanol
*Nitroso Compounds: BL, blood
Plasma: CH, chemistry
S-Nitrosoglutathione
*S-Nitrosothiols
Serum Albumin: ME, metabolism
Zinc Compounds: PD, pharmacology

RN 315-30-0 (Allopurinol); 51209-75-7 (S-nitrosocysteine); 52-90-4 (Cysteine); 52583-41-2 (acivicin); 57564-91-7 (S-Nitrosoglutathione); 60-24-2 (Mercaptoethanol); 67616-44-8 (S-nitrosomercaptoethanol); 70-18-8 (Glutathione); 7646-85-7 (zinc chloride)

CN 0 (Chelating Agents); 0 (Chlorides); 0 (Enzyme Inhibitors); 0 (Isoxazoles); 0 (Nitroso Compounds); 0 (S-Nitrosothiols); 0 (Serum Albumin); 0 (Zinc Compounds)

L3 ANSWER 23 OF 33 MEDLINE on STN

AN 2000241844 MEDLINE

DN PubMed ID: 10777705

TI Enhancement of S-nitrosylation in glycosylated hemoglobin.

AU Padron J; Peiro C; Cercas E; Llergo J L; Sanchez-Ferrer C F

CS Deparatamento de Farmacologia y Terapeutica, Facultad de Medicina, Universidad Autonoma de Madrid, Madrid, Spain.

SO Biochemical and biophysical research communications, (2000 Apr 29) 271 (1) 217-21.
Journal code: 0372516. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200006

ED Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000612

AB In this study, we report a novel differential **nitric oxide** interaction with nonglycosylated and glycosylated hemoglobin. After in vitro incubation of hemoglobin with S-nitroso N-acetyl penicillamine (SNAP), S-nitrosoglutathione, or S-nitrosocysteine, S-nitrosylation was significantly higher in human glycosylated hemoglobin purified from diabetic subjects compared to nondiabetic controls. Inversely, spontaneous decomposition was significantly lower for S-**nitrosohemoglobin** obtained from glycosylated hemoglobin. Bidimensional isoelectric focusing of hemoglobins incubated in vitro with SNAP also revealed a greater interaction of **nitric oxide** with glycosylated hemoglobin. In addition, a significantly higher level of S-**nitrosohemoglobin** was found in erythrocyte lysates from streptozotocin-induced diabetic rats compared to control rats. We suggest that highly glycosylated hemoglobin in diabetic subjects may favor S-nitrosylation, which may in turn impair vascular function, and participate in diabetic microangiopathy.

CT Check Tags: Human; In Vitro; Male; Support, Non-U.S. Gov't
Analysis of Variance
Animals
*Cysteine: AA, analogs & derivatives

Cysteine: ME, metabolism
Diabetes Mellitus, Experimental: BL, blood
Erythrocytes: ME, metabolism
*Hemoglobin A, Glycosylated: CH, chemistry
*Hemoglobin A, Glycosylated: ME, metabolism
Hemoglobins: ME, metabolism
Isoelectric Focusing
*Nitric Oxide: ME, metabolism
*Nitroso Compounds: ME, metabolism
Rats
Rats, Sprague-Dawley
*S-Nitrosothiols
Time Factors

RN 10102-43-9 (Nitric Oxide); 51209-75-7 (S-nitrosocysteine); 52-90-4 (Cysteine)

CN 0 (Hemoglobin A, Glycosylated); 0 (Hemoglobins); 0 (Nitroso Compounds); 0 (S-Nitrosothiols)

L3 ANSWER 24 OF 33 MEDLINE on STN

AN 2000334222 MEDLINE

DN PubMed ID: 10873557

TI S-nitrosothiol formation in blood of lipopolysaccharide-treated rats.

AU Jourd'heuil D; Gray L; Grisham M B

CS Center for Cardiovascular Sciences, Albany Medical College, Albany, New York 12208, USA.

NC DK 43785 (NIDDK)
DK 47663 (NIDDK)

SO Biochemical and biophysical research communications, (2000 Jun 24) 273 (1) 22-6.
Journal code: 0372516. ISSN: 0006-291X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200007

ED Entered STN: 20000810
Last Updated on STN: 20000810
Entered Medline: 20000727

AB The administration of the gram-negative bacterial cell wall component lipopolysaccharide (LPS) to experimental animals results in the dramatic up-regulation of the inducible form of **nitric oxide** synthase (iNOS). The resulting sustained overproduction of **nitric oxide** (NO) is thought to contribute to the septic shock-like state in these animals. Numerous studies have characterized the kinetics and magnitude of expression of iNOS as well as the production of NO-derived nitrite and nitrate. However, little is known regarding the ability of iNOS-derived NO to interact with physiological substrates such as thiols to yield biologically active S-nitrosothiols during endotoxemia. It has been hypothesized that these relatively stable, vaso-active compounds may serve as a storage system for NO and they may thus play an important role in the pathophysiology associated with endotoxemia. In the present study, we demonstrate that 5 h after i.p. administration of LPS in rats, circulating S-nitrosoalbumin was increased by approximately 3. 4-fold over control. S-**nitrosohemoglobin** was increased by approximately 25-fold over controls and by threefold over S-nitrosoalbumin. No increase in low molecular weight S-nitrosothiols (i.e., S-nitrosoglutathione and S-nitrosocysteine) could be detected under our experimental conditions. Taken together these data demonstrate that endotoxemia dramatically enhances circulating S-nitrosothiol formation.

CT Check Tags: Male; Support, U.S. Gov't, P.H.S.
Animals

Cysteine: AA, analogs & derivatives
Cysteine: BL, blood
Cysteine: ME, metabolism
Erythrocytes: CH, chemistry
Erythrocytes: DE, drug effects
Erythrocytes: ME, metabolism
Fluorescent Dyes: ME, metabolism
Glutathione: AA, analogs & derivatives
Glutathione: BL, blood
Glutathione: ME, metabolism
Hemoglobins: AN, analysis
Hemoglobins: ME, metabolism
*Lipopolysaccharides: TO, toxicity
*Mercaptoethanol
Molecular Weight
Nitrate Reductases: ME, metabolism
Nitrates: BL, blood
Nitrates: ME, metabolism
Nitric Oxide: ME, metabolism
Nitrites: BL, blood
Nitrites: ME, metabolism
*Nitroso Compounds: BL, blood
*Nitroso Compounds: ME, metabolism
Oxyhemoglobins: ME, metabolism
Rats
Rats, Sprague-Dawley
Reproducibility of Results
S-Nitrosoglutathione
*S-Nitrosothiols
Serum Albumin, Bovine: AN, analysis
Serum Albumin, Bovine: ME, metabolism

RN 10102-43-9 (Nitric Oxide); 51209-75-7 (S-nitrosocysteine); 52-90-4 (Cysteine); 57564-91-7 (S-Nitrosoglutathione); 60-24-2 (Mercaptoethanol); 67616-44-8 (S-nitrosomercaptoethanol); 70-18-8 (Glutathione)

CN 0 (Fluorescent Dyes); 0 (Hemoglobins); 0 (Lipopolysaccharides); 0 (Nitrates); 0 (Nitrites); 0 (Nitroso Compounds); 0 (Oxyhemoglobins); 0 (S-Nitrosothiols); 0 (S-nitrosoalbumin); 0 (S-nitrosohemoglobin); 0 (Serum Albumin, Bovine); EC 1.- (Nitrate Reductases); EC 1.7.99.4 (nitrate reductase)

L3 ANSWER 25 OF 33 MEDLINE on STN
AN 1999362704 MEDLINE
DN PubMed ID: 10430889
TI The oxyhemoglobin reaction of nitric oxide.
CM Comment in: Proc Natl Acad Sci U S A. 1999 Aug 31;96(18):9967-9. PubMed ID: 10468537
AU Gow A J; Luchsinger B P; Pawloski J R; Singel D J; Stamler J S
CS Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.
NC HL52529 (NHLBI)
HL59130 (NHLBI)
SO Proceedings of the National Academy of Sciences of the United States of America, (1999 Aug 3) 96 (16) 9027-32.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199909
ED Entered STN: 19990925
Last Updated on STN: 20000113
Entered Medline: 19990909

AB The oxidation of **nitric oxide** (NO) to nitrate by oxyhemoglobin is a fundamental reaction that shapes our understanding of NO biology. This reaction is considered to be the major pathway for NO elimination from the body; it is the basis for a prevalent NO assay; it is a critical feature in the modeling of NO diffusion in the circulatory system; and it informs a variety of therapeutic applications, including NO-inhalation therapy and blood substitute design. Here we show that, under physiological conditions, this reaction is of little significance. Instead, NO preferentially binds to the minor population of the hemoglobin's vacant hemes in a cooperative manner, nitrosylates hemoglobin thiols, or reacts with liberated superoxide in solution. In the red blood cell, superoxide dismutase eliminates superoxide, increasing the yield of S-**nitrosohemoglobin** and nitrosylated hemes. Hemoglobin thus serves to regulate the chemistry of NO and maintain it in a bioactive state. These results represent a reversal of the conventional view of hemoglobin in NO biology and motivate a reconsideration of fundamental issues in NO biochemistry and therapy.

CT Check Tags: Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Electron Spin Resonance Spectroscopy
Erythrocytes: PH, physiology
Kinetics
Models, Chemical
*Nitric Oxide: CH, chemistry
Nitric Oxide: ME, metabolism
*Oxyhemoglobins: CH, chemistry
Oxyhemoglobins: ME, metabolism
Spectrophotometry
Superoxides: BL, blood

RN 10102-43-9 (Nitric Oxide); 11062-77-4 (Superoxides)

CN 0 (Oxyhemoglobins)

L3 ANSWER 26 OF 33 MEDLINE on STN

AN 1999418447 MEDLINE

DN PubMed ID: 10489915

TI Nitric oxide metabolites in decompensated liver cirrhosis.

AU Barak N; Zemel R; Ben-Ari Z; Braun M; Tur-Kaspa R

CS Felsenstein Medical Research Center, Sackler School of Medicine, Tel Aviv University, Israel.

SO Digestive diseases and sciences, (1999 Jul) 44 (7) 1338-41.
Journal code: 7902782. ISSN: 0163-2116.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199909

ED Entered STN: 19991012
Last Updated on STN: 19991012
Entered Medline: 19990924

AB High levels of **nitric oxide** are thought to be the cause of some of the complications associated with decompensated end-stage liver disease. To assess **nitric oxide** metabolism in cirrhotic patients, we measured the levels of **nitric oxide** metabolites (**nitrosohemoglobin**, methemoglobin, nitrate, and nitrite) in normal subjects, in patients with decompensated cirrhosis, in patients with renal failure (model for impaired NO metabolites excretion), and in patients with mononitrates-treated anginal syndrome (model for exogenous **nitric oxide**). When compared to controls, patients with decompensated cirrhosis exhibited elevated levels of nitrate only. A significant increase of nitrate was also noted in patients receiving exogenous nitrates, whereas patients with impaired excretion had significantly elevated levels of both nitrite and

nitrate. In conclusion, **nitric oxide** metabolism in patients with decompensated cirrhosis is similar to that of patients receiving **nitric oxide** from an exogenous source. Renal impairment, whether alone or associated with cirrhosis, causes a change in **nitric oxide** metabolism. These findings may have clinical implications for nitrates treatment in patients with decompensated cirrhosis.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Aged
Angina Pectoris: BL, blood
Angina Pectoris: DT, drug therapy
*Hemoglobins: ME, metabolism
Kidney Failure, Chronic: BL, blood
*Liver Cirrhosis: BL, blood
Liver Cirrhosis: DI, diagnosis
*Liver Failure: BL, blood
Liver Failure: DI, diagnosis
*Methemoglobin: ME, metabolism
Middle Aged
*Nitrates: BL, blood
Nitrates: TU, therapeutic use
*Nitric Oxide: BL, blood
*Nitrites: BL, blood

RN 10102-43-9 (Nitric Oxide); 9008-37-1 (Methemoglobin)

CN 0 (Hemoglobins); 0 (Nitrates); 0 (Nitrites); 0 (S-nitrosohemoglobin)

L3 ANSWER 27 OF 33 MEDLINE on STN

AN 2000132519 MEDLINE

DN PubMed ID: 10669035

TI Evaluation of NOx in the cardiovascular system: relationship to NO-related compounds in vivo.

AU Ishibashi T; Yoshida J; Nishio M

CS Department of Pharmacology, Kanazawa Medical University, Uchinada, Ishikawa, Japan.

SO Japanese journal of pharmacology, (1999 Dec) 81 (4) 317-23. Ref: 34
Journal code: 2983305R. ISSN: 0021-5198.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 200002

ED Entered STN: 20000309
Last Updated on STN: 20000309
Entered Medline: 20000224

AB Diverse attention should be paid to evaluating NOx (NO2- and NO3-) in plasma as an index of endothelial **nitric oxide** (NO) formation in vivo. **Nitric oxide**, which subsequently appears as NOx, originates from different types of NO synthase and from nonenzymatic reactions. NOx also comes from exogenous sources such as food and gastrointestinal microorganisms. The fate of the NO incorporated into activation of guanylate cyclase, formation of nitrosyl hemoglobin (or **nitrosohemoglobin**), nitrosothiols, peroxynitrite and its derivatives and other possible compounds is not clear at present. However, some of these compounds would produce NOx as by-products or as final products through metabolism. Therefore, plasma NOx contains information about these pathways, although how extensively these factors contribute to plasma NOx has not been quantitatively defined. A theoretical simulation of NOx in the systemic circulation indicates that only small changes are expected by inhibition or stimulation of

endothelial NO production. Measuring NOx production during coronary circulation has the advantage that some degree of NOx accumulation is expected from intact endothelial cells because an excretion system is absent in the heart.

CT Check Tags: Human; Support, Non-U.S. Gov't
Animals
*Cardiovascular System: ME, metabolism
Endothelium, Vascular: ME, metabolism
*Nitrates: ME, metabolism
*Nitric Oxide: ME, metabolism
*Nitrites: ME, metabolism

RN 10102-43-9 (Nitric Oxide)

CN 0 (Nitrates); 0 (Nitrites)

L3 ANSWER 28 OF 33 MEDLINE on STN DUPLICATE 2

AN 2000086415 MEDLINE

DN PubMed ID: 10622703

TI In vitro formation of S-**nitrosohemoglobin** in red cells by inducible **nitric oxide** synthase.

AU Mamone G; Sannolo N; Malorni A; Ferranti P

CS Centro Internationale di Servizi di Spettrometria di Massa, CNR, Naples, Italy.

SO FEBS letters, (1999 Dec 3) 462 (3) 241-5.
Journal code: 0155157. ISSN: 0014-5793.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200002

ED Entered STN: 20000209
Last Updated on STN: 20000209
Entered Medline: 20000202

AB The present study demonstrates that NO produced in vitro by inducible **nitric oxide** synthase in red cells can convert hemoglobin contained in the red cells to S-**nitrosohemoglobin**. Experiments carried out either in the absence or in the presence of a low molecular weight thiol, such as cysteine, showed that in the first case the target of NO is heme-Fe2+. On the contrary, in the presence of cysteine, the first step is the formation of S-nitrosocysteine, followed by transfer of the NO group to a particular cysteine residue of beta-globin, cysteine 93. These results confirm previous data indicating the preferential formation of S-**nitrosohemoglobin** at that site by chemical methods [Ferranti et al. (1997) FEBS Lett. 400, 17-24], and the existence of a physiological mechanism of inactivation for NO circulating in blood. The analysis of S-**nitrosohemoglobin** can also allow the quantification of the NO levels in blood to be applied for in vitro and in vivo measurements.

CT Check Tags: Human; Support, Non-U.S. Gov't
Chromatography, High Pressure Liquid
Erythrocytes: EN, enzymology
*Erythrocytes: ME, metabolism
*Hemoglobins: BI, biosynthesis
Hemoglobins: CH, chemistry
Hemoglobins: ME, metabolism
*Mercaptoethanol
Nitric-Oxide Synthase: CH, chemistry
*Nitric-Oxide Synthase: ME, metabolism
Nitroso Compounds: CH, chemistry
Nitroso Compounds: ME, metabolism
Peptide Mapping
*S-Nitrosothiols
Spectrum Analysis, Mass

RN 60-24-2 (Mercaptoethanol); 67616-44-8 (S-nitrosomercaptoethanol)
CN 0 (Hemoglobins); 0 (Nitroso Compounds); 0 (S-Nitrosothiols); 0 (S-nitrosohemoglobin); EC 1.14.13.- (inducible nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L3 ANSWER 29 OF 33 MEDLINE on STN
AN 1998122360 MEDLINE
DN PubMed ID: 9462528
TI Cell-free and erythrocytic S-nitrosohemoglobin inhibits human platelet aggregation.
AU Pawloski J R; Swaminathan R V; Stamler J S
CS Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA.
SO Circulation, (1998 Jan 27) 97 (3) 263-7.
Journal code: 0147763. ISSN: 0009-7322.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199802
ED Entered STN: 19980306
Last Updated on STN: 19990129
Entered Medline: 19980223
AB BACKGROUND: **Nitric oxide** (NO) and related molecules are thought to inhibit human platelet aggregation by raising levels of cGMP. METHODS AND RESULTS: Both oxidative stress (reactive oxygen species) and hemoglobin (Hb) seem to oppose NO effects. A major fraction of NO in the blood is bound to thiols of Hb, forming S-**nitrosohemoglobin** (SNO-Hb), which releases the NO group on deoxygenation in the microcirculation. Here we show that (1) both cell-free and intraerythrocytic SNO-Hb (SNO-RBC) inhibit platelet aggregation, (2) the oxidation state of the hemes in Hb influences the response--SNO-metHb (which is functionally similar to SNO-deoxyHb) has greater platelet inhibitory effects than SNO-oxyHb, and (3) the mechanism of platelet inhibition by SNO-Hb is cGMP independent. CONCLUSIONS: We suggest that the RBC has evolved a means to counteract platelet activation in small vessels and the proaggregatory effects of oxidative stress by forming SNO-Hb.
CT Check Tags: Human
Blood Platelets: DE, drug effects
Blood Platelets: ME, metabolism
Cell-Free System
Cyclic GMP: BL, blood
Dose-Response Relationship, Drug
Erythrocytes: CH, chemistry
Erythrocytes: PH, physiology
*Hemoglobins: PD, pharmacology
Methemoglobin: AD, administration & dosage
Methemoglobin: PD, pharmacology
Oxyhemoglobins: PD, pharmacology
*Platelet Aggregation: DE, drug effects
Platelet Aggregation: PH, physiology
*Platelet Aggregation Inhibitors: PD, pharmacology
RN 7665-99-8 (Cyclic GMP); 9008-37-1 (Methemoglobin)
CN 0 (Hemoglobins); 0 (Oxyhemoglobins); 0 (Platelet Aggregation Inhibitors); 0 (S-nitrosohemoglobin)

L3 ANSWER 30 OF 33 MEDLINE on STN
AN 1998447444 MEDLINE
DN PubMed ID: 9776549
TI The effect of NO synthase inhibition on blood oxygen-carrying function during hyperthermia in rats.

AU Zinchuk V; Borisiuk M
CS Department of Physiology, Grodno Medical Institute, Belarus..
zinchuk@ggmi.belpak.grodno.by
SO Respiration physiology, (1998 Jul) 113 (1) 39-45.
Journal code: 0047142. ISSN: 0034-5687.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199812
ED Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981223
AB Hyperthermia is known to be accompanied by considerable worsening of body oxygen delivery. **Nitric oxide** (NO) is a messenger that contributes to the regulation of oxygen transport (vasodilation, formation of **nitrosohemoglobin**, erythrocyte deformability), but also has cytotoxic effects (when abundantly generated by inducible NO synthase and through a formation of peroxynitrite). The effects of NO synthesis inhibition on the blood oxygen transport (hemoglobin-oxygen affinity and erythrocyte deformability) were investigated in rats with hyperthermia. The most considerable changes in blood oxygen transport indices and the most pronounced hypoxia were observed in rats that received the NO synthase inhibitor N(omega)-nitro-L-arginine methyl ester (L-NAME) i.p. Its administration before heating significantly impaired body oxygen delivery, with a shift of the oxyhemoglobin dissociation curves rightwards and lowering of erythrocyte deformability. The changes in the blood oxygen transport in animals receiving L-arginine and L-NAME to prevent NO synthase inhibition were similar to those in rats treated with isotonic NaCl before heating.
CT Check Tags: Male
Animals
Enzyme Inhibitors: PD, pharmacology
Erythrocyte Deformability: DE, drug effects
*Fever: BL, blood
*Fever: EN, enzymology
NG-Nitroarginine Methyl Ester: PD, pharmacology
*Nitric-Oxide Synthase: AI, antagonists & inhibitors
*Oxygen: BL, blood
Oxyhemoglobins: AN, analysis
Rats
RN 50903-99-6 (NG-Nitroarginine Methyl Ester); 7782-44-7 (Oxygen)
CN 0 (Enzyme Inhibitors); 0 (Oxyhemoglobins); EC 1.14.13.- (endothelial constitutive nitric oxide synthase); EC 1.14.13.39 (Nitric-Oxide Synthase)

L3 ANSWER 31 OF 33 MEDLINE on STN
AN 97342849 MEDLINE
DN PubMed ID: 9197264
TI Blood flow regulation by S-nitrosohemoglobin in the physiological oxygen gradient.
AU Stamler J S; Jia L; Eu J P; McMahon T J; Demchenko I T; Bonaventura J; Gernert K; Piantadosi C A
CS Department of Medicine, Duke University Medical Center, Room 321 MSRB, Box 2612, Durham, NC 27710, USA.
NC HL 52529 (NHLBI)
HR59130 (NHLBI)
SO Science, (1997 Jun 27) 276 (5321) 2034-7.
Journal code: 0404511. ISSN: 0036-8075.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 199707
ED Entered STN: 19970724
Last Updated on STN: 20000303
Entered Medline: 19970716
AB The binding of oxygen to heme irons in hemoglobin promotes the binding of **nitric oxide** (NO) to cysteinebeta93, forming S-**nitrosohemoglobin**. Deoxygenation is accompanied by an allosteric transition in S-**nitrosohemoglobin** [from the R (oxygenated) to the T (deoxygenated) structure] that releases the NO group. S-**nitrosohemoglobin** contracts blood vessels and decreases cerebral perfusion in the R structure and relaxes vessels to improve blood flow in the T structure. By thus sensing the physiological oxygen gradient in tissues, hemoglobin exploits conformation-associated changes in the position of cysteinebeta93 SNO to bring local blood flow into line with oxygen requirements.
CT Check Tags: Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Animals
Blood Pressure
*Cerebrovascular Circulation
Cysteine: CH, chemistry
Cysteine: ME, metabolism
*Hemodynamic Processes
Hemoglobins: AN, analysis
Hemoglobins: CH, chemistry
*Hemoglobins: PH, physiology
*Mercaptoethanol
Models, Molecular
Nitric Oxide: BL, blood
Nitric Oxide: ME, metabolism
Nitroso Compounds: BL, blood
*Oxygen: BL, blood
Oxyhemoglobins: CH, chemistry
Protein Conformation
Rats
Rats, Sprague-Dawley
*S-Nitrosothiols
RN 10102-43-9 (Nitric Oxide); 52-90-4 (Cysteine); 60-24-2 (Mercaptoethanol); 67616-44-8 (S-nitrosomercaptoethanol); 7782-44-7 (Oxygen); 9008-02-0 (deoxyhemoglobin)
CN 0 (Hemoglobins); 0 (Nitroso Compounds); 0 (Oxyhemoglobins); 0 (S-Nitrosothiols); 0 (S-nitrosohemoglobin)

L3 ANSWER 32 OF 33 MEDLINE on STN
AN 1998042486 MEDLINE
DN PubMed ID: 9367862
TI S-nitrosohemoglobin in the fetal circulation may represent a cycle for blood pressure regulation.
AU Funai E F; Davidson A; Seligman S P; Finlay T H
CS Department of Obstetrics and Gynecology, New York University School of Medicine 10016, USA.
SO Biochemical and biophysical research communications, (1997 Oct 29) 239 (3) 875-7.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199712
ED Entered STN: 19980109
Last Updated on STN: 19980109
Entered Medline: 19971212
AB It has recently been demonstrated, in rats, that hemoglobin transports

nitric oxide (NO), as S-nitrosocysteine, from the lungs to the peripheral tissues. This cycle may be involved in the regulation of blood pressure and efficient delivery of oxygen in adult animals. We sought to determine whether this model was applicable to the human fetus. Umbilical cord blood was obtained from deliveries between 37 and 42 weeks of gestation (n = 19). NO, released from erythrocyte s-**nitrosohemoglobin** (SNO-Hb), was determined by the Saville reaction and total plasma NO was determined by the Greiss reaction. SNO-Hb levels were found to be higher in the umbilical vein, [SNO]/[Hb] = 2.19 +/- 1.22 (X10(-3)), than in the artery, [SNO]/[Hb] = 1.45 +/- 0.66 (X10(-3)) (P < 0.001, Wilcoxon Signed Rank test). This supports the hypothesis that fetal blood pressure may be regulated by erythrocytes acting via a hemoglobin-based mechanism.

CT Check Tags: Female; Human
Adult
*Blood Pressure
Fetal Blood: ME, metabolism
Fetal Blood: PH, physiology
*Fetus: BS, blood supply
Hemoglobins: ME, metabolism
*Hemoglobins: PH, physiology
Maternal-Fetal Exchange
Models, Biological
Nitric Oxide: BL, blood
Pregnancy
Umbilical Arteries
Umbilical Veins

RN 10102-43-9 (Nitric Oxide)

CN 0 (Hemoglobins); 0 (S-nitrosohemoglobin)

L3 ANSWER 33 OF 33 MEDLINE on STN

AN 94037326 MEDLINE

DN PubMed ID: 8222083

TI Metabolism and excretion of nitric oxide in humans. An experimental and clinical study.

AU Wennmalm A; Benthin G; Edlund A; Jungersten L; Kieler-Jensen N; Lundin S; Westfelt U N; Petersson A S; Waagstein F

CS Division of Clinical Physiology, Gothenburg University, Sahlgrenska Hospital, Sweden.

SO Circulation research, (1993 Dec) 73 (6) 1121-7.
Journal code: 0047103. ISSN: 0009-7330.

CY United States

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LA English

FS Priority Journals

EM 199312

ED Entered STN: 19940117
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AB Despite the increasing insight in the clinical importance of **nitric oxide** (NO), formerly known as endothelium-derived relaxing factor (EDRF), there is limited information about the metabolism and elimination of this mediator in humans. We studied the degradation of NO in healthy subjects inhaling 25 ppm for 60 minutes and in patients with severe heart failure inhaling 20, 40, and 80 ppm in consecutive 10-minute periods. In other healthy subjects, the renal clearance of NO metabolite was measured. The metabolism ex vivo was evaluated by direct incubation of nitrite, the NO oxidation product, in blood from healthy humans. During inhalation of NO, the plasma levels of nitrate increased progressively, both in the healthy subjects (from 26 to 38 mumol/L, P < .001) and in the patients (from 72 to 90 mumol/L, P < .001). Methemoglobin (MetHb) also increased in the healthy subjects (from 7 to 13

mumol/L, P < .001) as well as in the patients (from 19 to 42 mumol/L, P < .01). No change in **nitrosohemoglobin** (HbNO) was detected, either in the healthy subjects or in the patients. In arterialized blood (O2 saturation, 94% to 99%), incubated nitrite was semiquantitatively converted to nitrate and MetHb. In venous blood (O2 saturation, 36% to 85%) moderate amounts of HbNO were also formed. Plasma and urinary clearance of nitrate in healthy subjects averaged 20 mL/min. We conclude that uptake into the red blood cells with subsequent conversion to nitrate and MetHb is a major metabolic pathway for endogenously formed NO. Nitrate may then enter the plasma to be eliminated via the kidneys.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
Cardiac Output, Low: BL, blood
Cardiac Output, Low: ME, metabolism
Cardiac Output, Low: UR, urine
Kidney: ME, metabolism
Methemoglobinemia: BL, blood
Middle Aged
*Nitric Oxide: ME, metabolism
*Nitric Oxide: UR, urine
Nitrites: BL, blood
Reference Values

RN 10102-43-9 (Nitric Oxide)

CN 0 (Nitrites)